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Variation in Severity of Cardiac Disease in Holt-Oram Syndrome

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We describe a family with Holt-Oram syndrome (HOS) with variable hand and cardiac manifestations. One affected relative had complex congenital malformations of the heart consisting of an endocardial cushion defect and hypoplasia of the left ventricle. The literature from 1974 to 1995 is reviewed. Atrial septal defect is the most common cardiac abnormality (60.3% of 189 cases) occurring singly or in combination with other malformations. Thirty-three individuals (17.5% of literature cases) have more complex congenital malformations of the heart requiring complicated medical management and extensive cardiac surgery. Many genetic reference sources of HOS indicate that single or less severe cardiac malformations are expected in this disorder. It is important to provide more information about the occurrence and spectrum of severity of malformations of the heart to individuals and families where HOS is present.

KEY WORDS: Holt-Oram syndrome, familial cardiac malformations, hypoplastic left ventricle, thumb malformations

INTRODUCTION

Holt-Oram syndrome (HOS), also known as heart-hand syndrome, is an autosomal dominant condition involving thumbs, arms, and heart. The disorder is known to be highly penetrant with a marked variability in clinical expression [Basson et al., 1994; Gladstone and Sybert, 1982]. Recently, genetic analyses of several large pedigrees have demonstrated linkage of HOS to markers on 12q [Basson et al., 1994; Bonnet et al., 1994; Terrett et al., 1994], specifically 12q21-q3 [Bonnet et al., 1995]. At least one family with HOS does not show linkage to markers on 12q [Terrett et al., 1994; Basson et al., 1995] and thus HOS is likely to be heterogeneous [Terrett et al., 1994]. Variability of hand and arm malformations has been demonstrated previously. Cardiac malformations are very frequent in HOS (65–75% of affected individuals) and classically occur as single anomalies [Basson et al., 1994; Smith et al., 1979]. Here, we describe a family with HOS including a young boy with complex malformations of the heart. We have reviewed the literature from 1974 to 1995 to clarify the spectrum of expected cardiac malformations.

REPORTS OF PATIENTS

Patient 1 (IV-7) is a 19-month-old boy with hypoplasia of the left thumb (Fig. 1). He was born at term by cesarean section because of cephalopelvic disproportion; birth weight was 3.9 kg. At age 2 days, a murmur was first heard. Over the first 6 weeks of life, he developed tachypnea and sweating with feedings. At age 6 weeks, an echocardiogram showed complete atrioventricular canal with primum and secundum atrial septal defects, and very significant left ventricular hypoplasia with a hypoplastic mitral valve. There was narrowing of the aorta distal to the left subclavian artery similar to coarctation of the aorta, but without a gradient across the site. Also present were a large apical muscular VSD and a left superior vena cava connecting to the coronary sinus. Because of congestive heart failure, he underwent pulmonary arterial banding at 3 months. This was followed by a Damus-Kaye-Stanzel procedure with a central shunt at age 9 months. At age 15 months, his central shunt was removed and bilateral Glenn anastomoses were constructed. Currently, he is thriving, although more cardiac surgery will likely be necessary.

Patient 2 (III-7) is the 29-year-old mother of patient 1 (Fig. 2). As a child, a heart murmur was heard and she was followed with a diagnosis of small VSD at another institution. Evaluation here at 22 years showed the presence of triphalangeal thumbs with decreased thenar musculature (Fig. 3) and a grade ⅚ long systolic murmur heard best at the lower left sternal border. An echocardiogram documented a large secundum ASD, 3.8 cm in diameter at the time of surgical repair.

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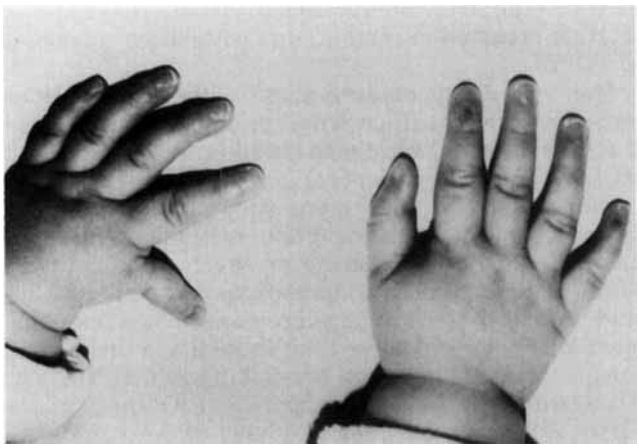

Fig. 1. Hands of patient 1 (IV-7). Hypoplasia of left thumb.

Patient 3 (III-8) is the 25-year-old sister of patient 2 who was examined when patient 2 was diagnosed with a secundum ASD. She also was found to have a large secundum ASD and underwent surgical repair. The defect measured 2.5 cm in diameter. The thumbs are normal, but there is mild hypoplasia of the thenar musculature.

Patient 4 (III-9) is the 27-year-old brother of patient 2. He has hypoplasia of the thenar musculature of the left hand. No cardiac anomaly has been found.

Patient 5 (II-4), the father of patients 2, 3, and 4 and the grandfather of patient 1, is a 51-year-old healthy man. He has triphalangeal thumbs with decreased thenar musculature of the left hand, without cardiac abnormality.

Patient 2 has a paternal first cousin (III-4) who has undergone ASD repair. A "double jointed" thumb is present by report. Two paternal second cousins (IV-1, IV-6) are said to have thumb anomalies. At present, these individuals are suspected to have HOS, but not confirmed.

METHODS AND RESULTS

The literature was reviewed from 1974 to 1995 to identify patients with Holt-Oram syndrome who had cardiac malformations. Reports detailing only hand malformations in individuals were not included. All patients with documented cardiac involvement were recorded. Patients were grouped (Table I) under those with single malformations, mild combinations, moderate combinations, and severe combinations. Mild combinations consisted of two or three coexistent malformations with mild clinical severity such as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus. Moderate combinations include such conditions as tetralogy of Fallot, endocardial cushion defect, or others which are more complicated in their need for surgical repair. Severe combinations include those conditions with worse clinical prognosis such as hypoplasia of the left heart, total anomalous pulmonary venous return, or truncus arteriosus where the threat to survival is substantial.

In this study, cardiac abnormalities were identified in 189 patients with HOS (Table I). Of these, 125 (66.1%) had a single abnormality such as ASD, VSD, or rarely others. ASD alone was found in 79 patients (41.8% of total) or it occurred in combination with other malformations in 35 patients (18.5% of total). Thus, in 60.3% of all patients with HOS, an ASD was found, either singly or coexistent with other malformations.

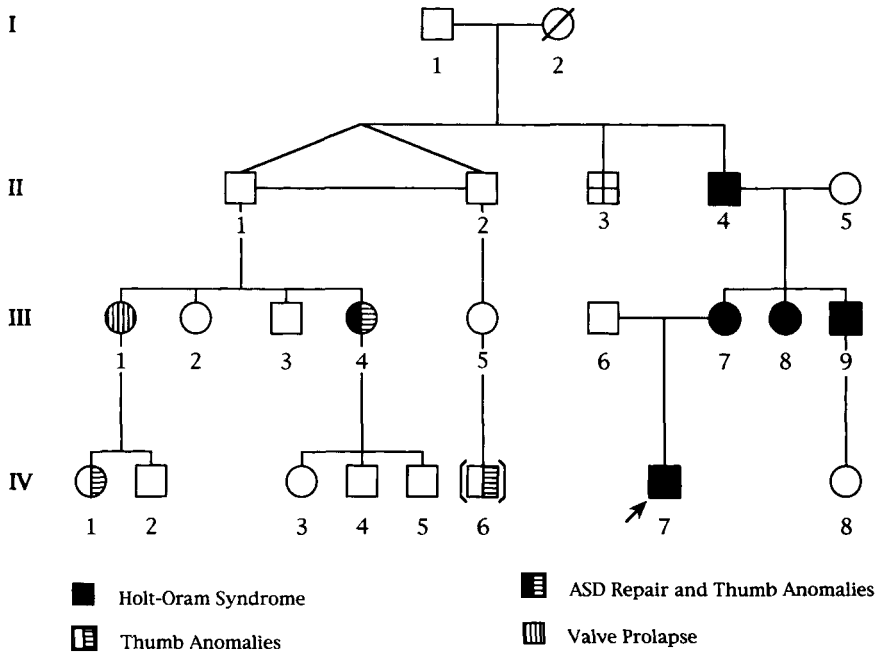

Fig. 2. Pedigree of family with Holt-Oram syndrome.

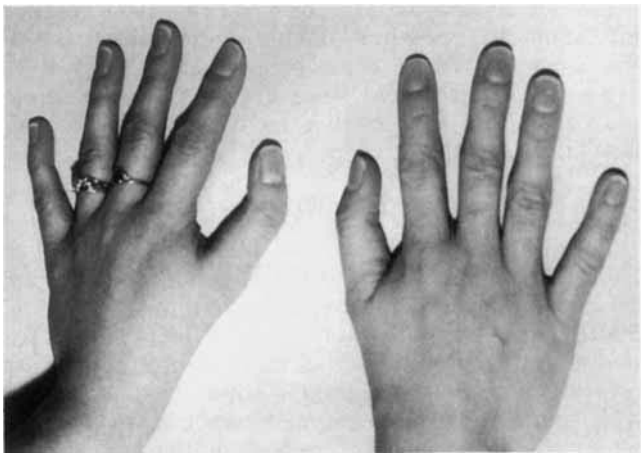

Fig. 3. Hands of patient 2 (III-7). Bilateral triphalangeal thumbs.

VSD was the sole malformation in 26 patients (13.8% of total) or occurred in combination with other anomalies in 7 (3.7%).

More significant malformations of the heart such as tetralogy of Fallot (6 patients) or endocardial cushion defect (8 patients) were also found in individuals with HOS. A total of 33 patients (17.5%) had cardiac malformations which required more complex surgical repair or had unknown prognosis. These patients are listed in Table I as having moderate or severe combinations. Those with moderate combinations (21 patients) include some whose cardiac surgery or medical management was more extensive than those listed under mild combinations. These were multiple muscular VSDs or Ebstein anomaly of the tricuspid valve. Of these 21 patients, 6 (28.6%) are known to have died, 11 are alive and the status of 4 is uncertain (Table I). Those with se-

TABLE I. Cardiac Abnormalities in 189 Previously Reported Patients With Holt-Oram Syndrome*

Single abnormalities	Mild combinations	Moderate combinations	Severe combinations
ASD: Unspecified (41) Secundum (37) Sinus venosus (1)	ASD, MVP (3)	ECD (Partial): • Primum ASD (2) • Primum ASD, cleft MV (1)	ASD, HLH (1)
VSD: Unspecified (23) Membranous (1) Muscular (2)	ASD, PDA (1)	ECD (Partial plus): • Primum ASD, Secundum ASD (1)	ASD, TAPVR (2)
MVP (3)	ASD, PS (2)	ECD (Complete): • ECD (3)	TA (2)
PDA (1)	ASD, PLSVC (2)	ASD, RAA with vascular ring formation, bicuspid pulmonic valve (1)	Complex cyanotic heart malformation (1)
PS (1)	ASD, APVR (1)	Ebstein's anomaly, ASD (1)	DORV, HLV (1)
HPA (1)	ASD, left intraventricular mass (1)	VSD (multiple muscular and membranous), PLSVC (1)	DORV, MA, HLV, RVOT obstruction, PLSVC (1)
Murmur (4)	ASD, RAA (1)	VSD (multiple muscular and membranous), APVR (1)	TAPVR (1)
Dextro (1)	ASD, VSD (muscular) (1)	VSD (multiple muscular and membranous), ASD, PDA, PLSVC (1)	TAPVR, complete AV block (1)
Conduction defect (5)	ASD, VSD (7)	VSD (multiple muscular), PDA, third degree AV block (1)	TAPVR, tricuspid atresia (1)
DPA (1)	ASD, VSD, PS (1)	VSD (3 muscular), ASD (1)	ECD (complete plus): • ECD, CA, LVOT obstruction (1)
Cardiomyopathy (1)	ASD, VSD, PDA (3)	TF, HPA (1)	
PLSVC (2)	ASD, VSD (muscular), PLSVC (1)	TF (3)	
	ASD, VSD, PS, dextro (1)	TF, ASD (2)	
	VSD, PLSVC (1)	DORV (1)	
	VSD, BAV (1)		
	VSD, PDA, ALCA (1)		
	VSD, PDA (1)		
	PDA, mitral insufficiency (1)		
	Unroofing coronary sinus interatrial communication, PLSVC (1)		
Total: 125[a]	Total: 31[b]	Total: 21[c]	Total: 12[d]

* ALCA, anomalous left coronary artery; APVR, anomalous pulmonary venous return; ASD, atrial septal defect; AV, atrioventricular; BAV, bicuspid aortic valve; CA, coarctation of the aorta; Dextro, dextroposition; DORV, double outlet right ventricle; DPA, dilated pulmonary artery; ECD, endocardial cushion defect; HLH, left heart hypoplasia; HLV, hypoplastic left ventricle; HPA, hypoplastic pulmonary artery; LVOT, left ventricular outflow tract; MA, mitral atresia; MV, mitral valve; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; PLSVC, persistent left superior vena cava; PS, pulmonary stenosis; RAA, right aortic arch; RVOT, right outflow tract; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TF, tetralogy of Fallot; VSD, ventricular septal defect.

[a] Reference numbers: 1, 3, 5, 6, 8, 12–15, 17–19, 21, 24–29, 33, 35, 37–42, 45–51, 53–56, 58, 60–63, 66.

[b] Reference numbers: 2, 6, 12, 16, 28, 32, 33, 35, 40, 43, 47, 48, 51, 66.

[c] Reference numbers: 4, 6, 17, 20, 22, 23, 35, 36, 38, 39, 41, 44, 48, 51, 57, 65.

[d] Reference numbers: 11, 17, 27, 29, 38–41, 52, 53, 62.

vere combinations of cardiac malformations include 12 patients (6.3% of total). The survival of this group is reduced because of the severity of their cardiac malformations. Six individuals (50.0%) of the severe group have expired, four are alive, and the status of two is uncertain. The total mortality of the patients with moderate or severe combinations of cardiac malformations is at least 36% (Table I).

DISCUSSION

Holt-Oram syndrome, described first by Holt and Oram in 1960, has a prevalence of 1/100,000 live births [Basson et al., 1994; Bonnet et al., 1994]. Variable clinical expression is evident in the extent of upper limb malformations. The affected structures, derived from the embryonic radial ray, include the radial, carpal, and metacarpal bones. Upper limb anomalies such as phocomelia, radial aplasia, thumb hypoplasia, absent thumbs, triphalangeal thumbs, and hypoplastic thenar muscles are all seen in HOS. Upper limb anomalies can be unilateral or bilateral.

Similarly, there is considerable variation in the cardiac malformations associated with the limb defects. Many textbooks and genetic reference sources which are widely used for genetic counseling [Jones, 1988; Goodman and Gorlin, 1983; Wiedemann et al., 1989] cite an ASD, VSD, and patent ductus arteriosus as the most common malformations associated with HOS. This study confirmed that ASD either alone or in combination with other cardiac malformations occurs most frequently (60.3% of patients). In addition, more than 17% of the patients with cardiac malformations reported from 1974 to 1995 had more complicated disease than expected from reading genetic reference texts. Such individuals usually have to undergo more complex surgical procedures than might be anticipated. In particular, more than 6% of the patients with HOS have very severe cardiac malformations with less favorable outcome (50% mortality).

It is important to provide insight into the severity of cardiac malformations to individuals and families with HOS. Since many affected individuals have ASD alone, the prognosis for this condition is excellent and surgical repair routine. This is not the case for more than 17% of the patients described who have moderate or severe combinations of cardiac malformations and more uncertain outcomes (28.6–50.0% mortality). Fetal echocardiography can be used to detect malformations in the offspring of an affected parent with HOS. Genetic counseling including discussion of the full spectrum of cardiac disease is warranted in HOS.

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